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Analysis of the Cyclin-Dependent Protein Kinases, cdk2 and cdk5, in the T cell Cycle

Leukemia results from the uncontrolled proliferation of cells of the immune system. Understanding the molecular basis of this disease requires knowledge of the biochemical machinery that controls the cell cycle. This proposal focuses on characterizing proteins from T lymphocytes that function in the regulation of proliferation. Protein kinases which bind to cellular proteins called cyclins, are thought to control cell cycle progression in most tissues. With the exception of $p34^{cdc2}$ (cdk1), this family of proteins have never been described from lymphocytes. We propose to isolate and characterize two of these protein kinases, cdk2 and cdk5, from activated mouse T cells. It is thought that these enzymes, when complexed to specific cyclins that are synthesized in the early stages of the T cell cycle, play an essential role in linking signals generated by external stimuli, such as specific antigen or T cell growth factors with the cell cycle machinery. We propose to examine the expression of these kinases and their associated cyclins, as well as their ability to phosphorylate proteins, as T cells progress from a resting or quiescent state into a proliferating state.

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Regulation of Lymphocyte Adhesion in Normal and Leukemic T Cells

The successful elimination of a foreign challenge by the body is dependent on a coordinated series of interactions between the various cell types in the immune system. Molecules on the cell surface termed integrins allow this cell-to-cell communication to occur, and other molecules on the cell surface regulate interaction. Defects in this regulation inside the cells or in the function of the integrin itself may be responsible for the development of T cell leukemias and other cancers. This project will examine the biochemical processes by which integrins are regulated on T lymphocytes. First, a cell surface molecule designated CD7 regulates integrin function in an undefined way. This proposal will investigate the role of an important class of intracellular enzymes, termed kinases, in the function of the CD7 molecule. Second, one integrin designated LFA-1 does not function in several cell lines derived from patients with T cell leukemia. This project will analyze why this integrin does not function in these leukemia cells. Since cell-to-cell contact and communication is critical in regulating T cell function, a better understanding of the regulatory mechanisms in normal T cells and the problems that seem to occur in tumor cells is necessary in order to devise improved strategies for detection and treatment of leukemias.